BSC Study Nomination Review

Meeting of the National Toxicology Program
Board of Scientific Counselors

National Institute of Environmental Health Sciences
Rall Building, Rodbell Conference Center
Research Triangle Park, NC

December 6, 2007

NTP Study Nomination: 2-methoxy-4-nitroaniline

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BSC Reviewers: Dr. Michael Pino and Dr. James Popp

1. Is a clear and valid rationale for the proposed research program articulated in the NTP research concept document?

   - The rationale for the proposed research program on 2-methoxy-4-nitroaniline is clear and valid based on its high production volume, potential for worker exposure, positive mutagenicity data, and the suspicion of carcinogenic activity based on structure activity relationships.

   - The weak part of the proposed research program is the very limited documentation of exposure.
     - The document repeatedly refers to "potential" for exposure but it is unclear whether substantial exposure occurs in the various settings where "potential" for exposure is suggested.

   - It was noted during the discussion that the 90 studies reporting an association between tattoos and skin cancer were primarily case reports; a clear association between tattoos and skin cancer has not been demonstrated by a controlled study.

2. Is the proposed research program as outlined in the research concept document appropriate in scope given the public health importance of the issue or substance proposed for study? Are there other studies that should be considered as part of this research program?

   - The proposed research program appears appropriate in scope given the public health importance of the compound.
     - The key aim of the research is to assess the toxicologic and carcinogenic potential of the compound (including effects on development and reproduction) in order to help assess human risk.

- The appropriate routes of exposure (inhalation and dermal) for the toxicology studies have been chosen based on the potential routes of human exposure.
- The Board is generally in favor of conducting a two-year carcinogenicity study only if deemed appropriate based on other study results, including results of mechanistic studies to look at DNA reactivity. However, all of the available information will need to be reviewed before this assessment can be made.
- The appropriate target tissues to be used for the DNA reactivity studies will need to be identified, but tissue distribution studies may help in making this selection.
- The focus on identification of metabolites is appropriate and should be given high priority. Two additional points related to metabolism should be considered:
  - Animal and human metabolite comparisons (using in vitro approaches) should be included in the plan.
  - Urinary metabolites should be determined in the toxicology species to provide a basis for later human comparisons.
- Mechanisms of potential muscle and cardiac toxicity should be considered prior to initiation of subchronic studies. Additional endpoints should be included in the planned standard studies to address mechanism of toxicity if appropriate.

3. Does the proposed research program address an important area of biomedical research (e.g. children's health, genetic susceptibility, specific environmental disease) and/or advance the field of environmental health sciences?

- The proposed research addresses an important area of environmental health due to the high production and use of 2-methoxy-4-nitroaniline and the potential for human exposure.
- The proposed studies could provide additional information on structure activity relationships of toxicity but only with a thorough assessment of metabolites.

4. Does the proposed research program merit utilization of NTP resources, and if so, what priority (low, moderate, or high) should it be given?

- The proposed research program merits utilization of NTP resources given the potential for human exposure.
  - Although occupational exposure to 2-methoxy-4-nitroanaline is low, the occupational exposure to Yellow Dye 74 is higher. It was clarified during the meeting that Yellow Dye 74 can undergo photo decomposition to yield 2-methoxy-4-nitroanaline.
  - There is potential for the general population to be exposed to small quantities of 2-methoxy-4-nitroanaline through consumer and environmental sources.
- The priority of this program should be moderate to high.

Date: December 18, 2007